Maintenance of Acute Stroke Care Service During the COVID-19 Pandemic Lockdown

Altersberger, Valerian L ; Stolze, Lotte J ; Heldner, Mirjam R ; Henon, Hilde ; et al ; Baumgartner, Philipp ; Wegener, Susanne

Abstract: [Figure: see text].

DOI: https://doi.org/10.1161/STROKEAHA.120.032176

American Stroke Association.
A division of the American Heart Association.

Stroke

Manuscript Submission and Peer Review System

URL: http://stroke-submit.aha-journals.org

Title: Effect of admission time on provision of acute stroke treatment at Stroke Units and Stroke Centres

Manuscript number: STROKE/2021/036157

Author(s): Valerian Altersberger, Patrick Wright, Sabine Schaedelin, Gian Marco De Marchis, Henrik Gensicke, Stefan Engelter, Marios-Nikos Psychogios, Timo Kahles, Martina Goeldlin, Thomas Meinel, Pasquale Mordasini, Johannes Kaesmacher, Alexander von Hessling, Jochen Vehoff, Johannes Weber, Susanne Wegener, Stephan Salmen, Rolf Sturzenegger, Friedrich Medlin, Christian Berger, Ludwig Schelosky, Susanne Renaud, Julien Niederhäuser, Christophe Bonvin, Michael Schaerer, Marie-Luise Mono, Biljana Rodic, Guido Schwegler, Nils Peters, Manuel Bolognese, Andreas Luft, Carlo Cereda, Georg Kägi, Patrik Michel, Emmanuel Carrera, Marcel Arnold, Urs Fischer, Krassen Nedeltchev, and Leo Bonati

Effect of admission time on provision of acute stroke treatment at Stroke Units and Stroke Centres

Valerian L Altersberger, MD[1]; Patrick R Wright, PhD[2]; Sabine A Schaedelin, PhD[2]; Gian Marco De Marchis, MD[1]; Henrik Gensicke, MD[1,3]; Stefan T Engelter, MD[1,3]; Marios Psychogios, MD[4]; Timo Kahles, MD[5]; Martina Goeldlin, MD[6]; Thomas R Meinel, MD[6]: Pasquale Mordasini, MD[7]; Johannes Kaesmacher, MD[7]; Alexander von Hessling, MD[8]; Jochen Vehoff, MD[9]; Johannes Weber, MD[9]; Susanne Wegener, MD[10]; Stephan Salmen, MD[11]; Rolf Sturzenegger, MD[12]; Friedrich Medlin, MD[13]; Christian Berger, MD[14]; Ludwig Schelosky, MD[15]; Susanne Renaud, MD[16]; Julien Niederhauser, MD[17]; Christophe Bonvin, MD[18]; Michael Schaerer, MD[19]; Marie-Luise Mono, MD[20]; Biljana Rodic, MD[21]; Guido Schwegler, MD[22]; Nils Peters, MD[23]; Manuel Bolognese, MD[8]; Andreas R Luft, MD[10,24]; Carlo W Cereda, MD[25]; Georg Kägi, MD [6,9]; Patrick Michel, MD[26]; Emmanuel Carrera, MD[27] Marcel Arnold, MD[6]; Urs Fischer, MD[6]; Krassen Nedeltchev, MD[5]; Leo H Bonati, MD[1]

On behalf of the Swiss Stroke Registry Investigators

Affiliations:

1. Stroke Center and Department of Neurology, University Hospital Basel and University of Basel, Switzerland
2. Clinical Trial Unit, University Hospital Basel and University of Basel, Switzerland
3. Neurorehabilitation, University of Basel and University Department of Geriatic Medicine FELIX PLATTER, University of Basel, Switzerland
4. Department of Neuroradiology, University Hospital Basel and University of Basel, Switzerland
5. Department of Neurology, Kantonsspital Aarau, Switzerland

6. Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Switzerland
7. University Institute of Diagnostic and Interventional Neuroradiology and University Institute of Diagnostic, Interventional and Paediatric Radiology, Inselspital, Bern University Hospital Inselspital Bern, and University of Bern, Switzerland
8. Cantonal hospital Lucerne, Switzerland
9. Department of Neurology, Kantonsspital St. Gallen, Switzerland
10. Department of Neurology, University Hospital Zurich and University of Zurich, Switzerland
11. Department of Neurology, Spitalzentrum Biel, Switzerland
12. Cantonal hospital Graubuenden, Switzerland
13. Department of Internal Medicine, Stroke Unit and Division of Neurology, HFR Fribourg – Cantonal Hospital, Fribourg, Switzerland
14. Stroke Unit, Hospital Grabs, Switzerland
15. Cantonal hospital Muensterlingen, Switzerland
16. Stroke unit and division of neurology, Neuchatel Hospital Network, Switzerland
17. Stroke unit, Hôpital Nyon, Switzerland
18. Spital Sion, Switzerland
19. Bürgerspital Solothurn, Switzerland
20. Stadtspital Triemli Zürich, Switzerland
21. Cantonal hospital Winterthur, Switzerland
22. Spital Limmattal, Switzerland
23. Stroke Center, Hirslanden Hospital Zurich, Switzerland
24. Cereneo Center for Neurology and Rehabilitation, Weggis, Switzerland
25. Stroke Center and department of Neurology, Neurocenter of Southern Switzerland, Lugano, Switzerland

26. Department of Neurology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland
27. Department of Neurology, HUG Geneve, Switzerland

Correspondence to:

Prof. Leo Bonati

Department of Neurology

University Hospital Basel

Petersgraben 4

CH – 4031 Basel

Phone: +41615565442

E-mail: leo.bonati@usb.ch

Cover title: Effect of admission time on acute stroke treatment

Whole Manuscript: 5995

References: 30

Figures: Figure 1-3

Tables: Table 1-3

Supplemental material: Supplemental Table I-II, Supplemental Appendix

Abstract

Background and Purpose: Rapid treatment of acute ischemic stroke (AIS) depends on sufficient staffing which differs between Stroke Centres and Stroke Units in Switzerland. We studied the effect of admission time on performance measures of AIS treatment and related temporal trends over time.

Methods: We compared treatment rates, door-to-image-time, door-to-needle-time, and door-to-groin-puncture-time in stroke patients admitted during office hours (Monday-Friday 8:00-17:59) and non-office hours at all certified Stroke Centres and Stroke Units in Switzerland, as well as secular trends thereof between 2014 and 2019, using data from the Swiss Stroke Registry. Secondary outcomes were modified Rankin Scale and mortality at 3 months.

Results: Treatment rates for IVT/EVT were higher during non-office hours compared with office hours in Stroke Centres (40.8 vs 36.5%) and Stroke Units (21.8 vs 18.5%). Door-to-image-time and door-to-needle-time increased significantly during non-office hours. Door-to-groin-puncture-time at Stroke Centres was longer during non-office hours compared to office hours (95 vs 84 minutes). Admission during non-office hours was independently associated with worse functional outcome and increased mortality. From 2014 to 2019, median door-to-groin-puncture-time improved from 112 to 84 minutes and the treatment rate for wake-up strokes increased from 13 to 32%.

Conclusions: Despite differences in staffing, patient admission during non-office hours delayed IVT to a similar, modest degree at Stroke Centres and Stroke Units. A larger delay of EVT was observed during non-office hours, but Stroke Centres sped up delivery of EVT over time. Patients admitted during non-office hours had worse functional outcomes, which was not explained by treatment delays.

Non-standard Abbreviations and Acronyms

IVT: intravenous thrombolysis

EVT: endovascular therapy

sICH: symptomatic intracranial hemorrhage

SSR: Swiss Stroke Registry

CTU: Clinical Trial Unit

DIT: door-to-image-time

DNT: door-to-needle time

DPT: door-to-groin-puncture time

OH: office hours

NH: non-office hours

Introduction

Intravenous thrombolysis (IVT) and endovascular recanalization therapy (EVT) reduce disability in patients with acute ischemic stroke (AIS) (1,2). Rapid delivery of treatment is crucial and depends – among other factors – on the presence of experienced staff and access to infrastructure. In addition, acute stroke care has become more and more complex due to recent extension of time windows and imaging eligibility criteria in both IVT- and EVT-treated patients (3,4). Furthermore, according to most stroke guidelines patients presenting with so called wake-up strokes can also benefit from acute reperfusion therapies depending on certain imaging features (5,6,7). These aspects represent a considerable challenge for staff involved in the acute treatment of AIS.

However, staff levels and availability of infrastructure may vary depending on time of the day and day of the week, and differ between Stroke Centres and Stroke Units. In Switzerland, certification guidelines require a 24/7 attendance of a stroke neurologist at Stroke Centres whereas an on-call service is permitted at night and on weekends at Stroke Units following the guidelines of the *European Stroke Organisation* (8). Understanding the effect of day and time of admission on delivery and functional outcome of acute stroke care is relevant for service providers and health policy makers.

Previous research on the effect of admission during “office-hours” versus “non-office hours” on the speed of delivery and outcomes of IVT was done in heterogeneous settings and yielded controversial results (9-13). Importantly, most of the previous research investigated patient cohorts when neither EVT per se, nor reperfusion treatment for AIS in the extended time window were widely implemented in everyday practice. The increasing proportion of stroke patients receiving EVT poses greater demands on staff and infrastructure. As of now, little is known on circadian and weekday variation of the speed of delivery and outcome of EVT.

In order to consolidate and extend the evidence on diurnal and weekday variations of acute stroke treatment and to examine possible changes following recent modifications in

therapeutic concepts, we conducted the present study using prospectively collected data from the Swiss Stroke Registry (SSR) between 01/2014 and 12/2019.

Methods

According to the AHA Journals' implementation of the Transparency and Openness Promotion Guidelines, all data and materials can be accessed by request from the corresponding author (valerian.altersberger@usb.ch).

Study design

For this cohort study, we used prospectively collected data from the *Swiss Stroke Registry* (SSR). The SSR is a national web-based registry designed to facilitate multi-centric research in acute stroke and assure the provision and quality of acute stroke care in Switzerland, which started in January 2014 (14). The registry collects a standardized dataset of all patients with acute stroke, TIA and other acute cerebrovascular events including a follow-up assessment after 3 months. The registry is compulsory for all hospitals certified as Stroke Units or Stroke Centres in Switzerland, in line with the *European Stroke Organisation* criteria (15). The database is managed by the Clinical Trial Unit (CTU) of the University of Basel. Data collection is done locally in each Stroke Centre/ each Stroke Unit. All patients with ischemic stroke admitted between 01.01.2014 and 31.12.2019 were included.

Parameters of interest for the present study were age, sex, National Institutes of Health Stroke Scale (NIHSS) score (16), date and time of stroke onset (or last seen well), of hospital admission, of first image and of treatment initiation (IVT and/or EVT), presence of wake up stroke, blood pressure prior to IVT treatment, glucose levels in blood serum on admission, vascular risk factors according to predefined criteria (17) and prior treatment with anticoagulation as well as pre-stroke functional status measured by the modified Rankin Scale (mRS) (18). Wake-up stroke is defined as a stroke with symptoms that were present when the

patient awoke but not prior to falling asleep. Clinical data, neurologic and functional outcomes during hospitalization and at 3 months after stroke were also collected. Clinical evaluations, as well as NIHSS and mRS assessments, were performed by certified stroke neurologists as part of their clinical activity. If an in-person visit was not possible at 3 months, mRS score was assessed by a phone interview with mRS-trained examiners.

Outcomes

Primary outcomes were the rate of patients with acute reperfusion therapy (i.e. the proportion of patients with AIS receiving IVT and/or EVT) and in-hospital performance measures in patients receiving IVT and/or EVT), defined as the following time intervals: (i) from hospital admission to brain imaging in IVT/EVT ("door-to-image-time" (DIT)) (ii) from hospital admission to start of IVT ("door-to-needle time" (DNT)) (iii) from hospital admission to start of EVT ("door-to-groin-puncture time" (DPT)). EVT is exclusively performed in Stroke Centres in Switzerland. As secondary outcomes, we investigated functional status defined by the mRS, as well as mortality at 3 months.

Statistical analyses

Statistical analyses were performed with R version 3.6.3 (*R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/*). The database is implemented in the commercial software secuTrial (interActive Systems GmbH, Germany) and is managed by the Clinical Trial Unit (CTU) of the University of Basel aided by the secuTrialR package (19).

We investigated differences in primary and secondary outcomes between patients admitted during "office hours" (OH) (Monday-Friday 8:00-17:59) and patients admitted during "non-office hours" (NH) (Monday-Friday 18:00-07:59, Saturday, Sunday, national holidays), at

Stroke Centers and Stroke Units separately. Continuous data were summarized as median and interquartile range (IQR). We compared the rates of acute reperfusion therapy using Chi2-test and the performance measures using Wilcoxon test. Performance measures during OH and NH were additionally compared using a linear mixed model where the respective center was included as random effect. Performance measures were log-transformed to better meet the normality assumption.

The association between admission time and functional outcome as well as mortality was estimated by calculating odds ratios (OR) with 95% confidence intervals (95% CI), using ordered logistic regression models and binary logistic regression, respectively. Analyses were done both unadjusted and adjusted for baseline NIHSS, age, pre-stroke mRS, and stroke-onset-to-treatment time (for patients receiving acute reperfusion therapy). Patients with missing data on the mRS at 3 months were excluded. Furthermore, we evaluated the change over time from 2014 until 2019 regarding in-hospital performance measures (DIT, DNT, DPT) to investigate any learning curve effects in Stroke Units and Stroke Centres separately in descriptive analyses. Performance measures displayed as median and IQR were analysed each year beginning in 01/2014. Patients referred to hospital with symptoms of wake-up stroke as well as patients with in-hospital strokes were excluded from these analyses.

As an exploratory analysis, we also investigated the rate of patients treated with IVT or EVT for wake-up strokes for each year.

Role of the funding source/ Ethics

No sponsor was involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

The study complied with the Declaration of Helsinki. The study was classified as a Quality Assurance Study by the responsible ethics committee and the necessity for formal review was

waived. In accordance with national law, patients were informed about the use of their routinely collected data for research purposes. Patients who denied use of their data were excluded from the analysis. Anonymized data will be shared on request from any qualified investigator. The analysis code is available on GitHub: *https://github.com/PatrickRWright/Publications_code*

Results

Data were eligible for analysis in 31'788 (90.2%) of 35'261 AIS patients. Reasons for excluding patients were missing data on DIT, DNT or DPT (n = 3'473; 9.8%).

Baseline characteristics

11'844 patients (48.7%) were admitted during office-hours (OH) and 12'471 (51.3%) during non-office hours (NH) in Stroke Centres. In Stroke Units, 3'919 (52.4%) arrived during OH and 3'554 (47.6%) during NH. Overall, there was no substantial difference in characteristics of AIS patients arriving during OH and those arriving during NH: age, sex, stroke severity, pre-stroke disability as well as the prevalence of cardiovascular risk factors were similar between groups. Stroke-onset-to-admission time was higher during OH in Stroke Centres and Stroke Units (**Table 1**). Among patients receiving acute reperfusion therapy, baseline characteristics were evenly distributed (**Supplemental Table I**).

Patients in Stroke Centres had higher baseline stroke severity, were more likely to suffer from atrial fibrillation and more frequently under anticoagulation at the time of their stroke than patients treated in Stroke Units (**Table 1**).

Primary outcomes: Rate of acute reperfusion therapy and in-hospital performance measures

Patients with AIS arriving during NH at Stroke Centres received acute reperfusion therapy with IVT or EVT more often than during OH (40.8% vs. 36.5%, p<0.001). Likewise, patients being admitted during NH to Stroke Units were more likely to be treated with IVT than during OH (NH 21.8% vs. OH 18.5%, p<0.001) (**Table 2**).

Median DIT in patients treated with acute reperfusion therapy was faster during OH: Stroke Centres, DIT 23 vs 22 minutes, p<0.001; Stroke Units, DIT 19 vs 17 minutes; p<0.01. Fittingly, median DNT was significantly increased in patients arriving during NH compared to arriving during OH, both at Stroke Centres (43 vs 37 minutes, p<0.001) and Stroke Units (45 vs 39 minutes, p<0.001). Median DPT at Stroke Centres was longer in patients arriving during NH compared to OH (95 vs 84 minutes, p<0.001) (**Table 2**).

The time differences between OH and NH for each primary outcome remained significant after calculating a linear mixed model with Stroke Centre or Stroke Unit included as random effect (**Supplemental Table II**).

Secondary outcomes: Functional outcome and mortality

After adjustment for age, baseline NIHSS and pre-stroke mRS, AIS patients arriving during NH in Stroke Centres had 1.11 (95% CI 1.04-1.18) times the odds of having a worse functional outcome at three months and OR 1.13 (95% CI 1.01-1.27) times the odds for mortality at 3 months compared with arriving during OH. Admission during NH in Stroke Units also increased the odds for worse functional outcome (1.12 (95% CI 0.99-1.26)) and mortality (1.15 (95% CI 0.89-1.49)) at 3 months without reaching statistical significance.

Among patients receiving acute reperfusion therapy, admission during NH was again associated with worse outcome (1.18 (95% CI 1.07-1.31)) and mortality (1.18 (95% CI 1.01-1.38)) at 3 months in Stroke Centres, after adjustment for patient characteristics and onset-to-treatment time. At Stroke Units, arrival during NH increased the point estimate similarly for

worse outcome (1.12 (95% CI 0.87-1.46)) and mortality (1.48 (95% CI 0.89-2.47)) without reaching statistical significance (**Table 3**, **Figure 1**).

Temporal trends in performance measures and treatment of wake-up strokes

The median DIT for patients with acute reperfusion therapy remained relatively constant from 2014 to 2019 at Stroke Centres and Stroke Units. Similarly, the median DNT remained relatively stable (Stroke Centre: 2014 39 vs 2019 40 minutes; Stroke Unit: 2014 38 vs 2019 40 minutes). However, a considerable decrease of DPT at Stroke Centres (2014 112 vs 2019 84 minutes) over time became apparent (**Figure 2**).

The probability for acute reperfusion treatment of wake-up stroke with IVT and/ or EVT increased over time from 13.2% in 2014 to 25.0% in 2016, and to 31.7% in 2019 (**Figure 3**).

Discussion

Our study showed the following key results regarding the impact of day and time of admission on in-hospital performance measures and functional outcomes in ischemic stroke patients: (i) Despite differences in staffing, the speed of IVT was affected to a similar, modest degree by day and time of admission at Stroke Centres and Stroke Units. (ii) The initiation of EVT in Swiss Stroke Centres is delayed when being admitted during NH. (iii) Admission during NH is associated with worse outcome and increased mortality at 3 months independent of patient characteristics and delays in treatment delivery. (iv) Over time (2014-2019), the speed of delivery of EVT as well as the treatment rate for wake up strokes have increased.

In our study population about 50% of all ischemic stroke patients were admitted during NH, where the rate of acute reperfusion therapy (IVT or EVT) turned out to be higher than during

OH, both at Stroke Centres (40.8% vs 36.5%) and Stroke Units (21.8% vs 18.5%). We observed that AIS patients were admitted considerably faster during NH than during OH, which may have contributed to the higher reperfusion therapy rate.

We found a statistically significant delay in delivery of IVT during NH, both at Stroke Centres and Stroke Units. Previous studies on diurnal variations of service provision in acute stroke treatment have yielded inconsistent results: A Swedish study found that DNT within 30 minutes was less likely during NH (12). In line, Reuter et al. found the longest DNT time and the lowest IVT rate between 03:01 and 06:00 am (9). Furthermore, Kristiansen et al. found in-hospital performance measures overall – but not thrombolysis rates – to be worse in patients admitted during NH (20). Other studies, however, showed no association of DNT with time of hospital arrival (11) and no deterioration of acute reperfusion therapy rates in candidates for thrombolytic therapy (21).

Differences in staffing of emergency and radiology departments (independent of acute stroke services) might contribute to the higher DNT during NH by delaying image acquisition and decision-making (12). However, the delays in DIT in the present study during NH were very minor (median DIT: Stroke Centres: 23 vs 22 minutes; Stroke Units 19 vs 17 minutes). Some studies have also reported that patients admitted during NH may have more severe strokes and more comorbidities, potentially rendering treatment decisions more difficult (12,22). Yet in our study, baseline characteristics regarding comorbidities and stroke severity were well balanced between patients arriving during OH and NH. Another contributing factor to longer DNT during NH could be the experience of the treating physician and the availability of treating specialised stroke-neurologist. As there is little difference in DIT between NH and OH, the procedural step most sensitive to delay during NH appears to be the decision whether to administer IVT. In Stroke Units the treating physician is obliged to make contact with the on-call neurologist during NH which takes additional time. In Stroke Centres, certification

criteria in Switzerland require a 24/7 presence of a stroke neurologist. Despite these differences in staff requirements, the delay in DNT during NH compared with OH was similar at Stroke Centres (median 43 vs 37 minutes) and Stroke Units (45 vs 39 minutes), and only moderate in extent. It has to be noted that patients admitted to Stroke Centres for IVT were more likely to take oral anticoagulation than patients treated at Stroke Units, which may cause additional delays in treatment during NH, depending on the availability of coagulation tests.

Regarding the speed of EVT at Stroke Centres, we found a substantial, 11 minute in-house treatment delay during NH compared with admission during OH (median DPT 95 vs 84 minutes). To date, only a few studies have investigated the impact of admission time on DPT: One study analysing data from 2013-2014 found longer door-to-reperfusion times for patients admitted during night-time and weekends in a small sample size (n=98) (23). Another study (n=189) reported significantly longer image-to-treatment times during NH (24). Recently, it was suggested that EVT in the morning is associated with good and EVT at the end of the workday with poor functional outcome (25). In the same study DPT was also increased during nighttime. Optimising EVT performance during NH is crucial because it has already been suggested that the majority of EVTs occur during NH, when transfer to hospital was reported to be delayed (24, 26). EVT is a staff-intensive procedure that requires presence of nurses, medical technical assistants, anaesthesiologists and neurointerventionalists. Furthermore, during NH the neurointerventionalist and other on-call staff have to travel to the hospital from home, in most settings (27). Overall, we observed a clear reduction in DPT over the years, indicating that Stroke Centres have continuously optimised their in-house procedures to deliver EVT (**Figure 2**). The same secular trend could not be observed for DNT, possibly indicating a certain ceiling effect in the way that IVT pathways were already optimised at the beginning of the capture period. However, counteracting trends prolonging DNT must also be considered, such as the increasing proportion of patients on oral anticoagulation receiving IVT after emergency coagulation checks (which take time) (28). Furthermore, Stroke Centres

and Stroke Units appear to have quickly adopted the recent evidence and treatment recommendations for wake-up stroke, indicated by a more than doubling in the proportion of patients with wake-up stroke receiving acute recanalization therapy from 2014 (13.41%) to 2019 (31.7%) (**Figure 3**).

Admission during NH resulted in higher odds for worse outcome and mortality in ischemic stroke patients similar to other studies investigating outcomes of patients suffering from AIS as well as other diseases during NH (12,13,29). This effect was not accounted for by differences in measured patient characteristics, rates of or delays in recanalization therapy. Factors such as the start of secondary prevention, availability of dysphagia screening, access to diagnostic tests and recognition of early complications may contribute to a true worsening in functional outcome when patients are admitted during NH. However, it is also possible that differences in unmeasured characteristics between patients admitted during NH and those admitted during OH may have caused residual confounding. E.g., diurnal variations in haemostasis, inflammation and cardiac biomarkers have been described (30).

Strengths and Limitations

One strength of the present study is the large sample size (n=35'261) with low number of missing data on primary outcomes (9.8%). Previous studies regarding EVT during NH were much smaller in comparison to the EVT sample size of the present study (n=4'183). Furthermore, data collection was performed from 01/2014 up to 12/2019 resulting in up-to-date analyses reflecting the current situation of real world stroke service provision. Due to the timespan of 6 years we were able to investigate temporal trends such as learning curve effects after implementation of major modifications in acute stroke care.

Our study has some limitations: Apart from general limitations of registry based, retrospective studies we were unable to clarify why performance measures and outcomes are worse during

NH and can only make assumptions. It is possible that unmeasured differences between OH and NH were missed in patients or settings, leading to residual confounding. Also, our results may not be generalizable to countries with more limited availability of infrastructure and staff.

Summary/ Conclusions

The delivery of acute recanalization therapy at Swiss Stroke Centres and Stroke Units is moderately delayed during non-office hours. Patients admitted during NH have a worse functional outcome which is not explained by availability or delay of recanalization therapy. Recent evidence and recommendations for treatment of wake-up stroke have been quickly adopted over the past few years. Overall, our findings show that Stroke Centres and Stroke Units certified in accordance to European guidelines are capable of providing round-the-clock acute stroke care, which may inform the planning of service provision in other health care systems.

Disclosures

VLA, SAS, PRW, MP, TK, AvH, TM, EC, SS, RS, JV, JN, LS, SR, MS, MLM, BR, GS report no disclosure.

GMDM has received support from the Swiss National Science Foundation; Spezialprogramm Nachwuchsförderung Klinische Forschung, University of Basel; Science Funds of the University Hospital Basel; Swiss Heart Foundation; Bangerter-Rhyner-Stiftung; Swisslife Jubiläumsstiftung for Medical Research; Swiss Neurological Society; Fondazione Dr Ettore Balli; De Quervain research grant; Thermo-Fisher-GmbH; consultant honoraria by Bayer; speaker honoraria by Medtronic and BMS/Pfizer.

HG has received research support from the Swiss National Science Foundation, advisory board honoraria from Daiichi-Sankyo and funding for travel from BMS/Pfizer.

STE has received funding for travel or speaker honoraria from Bayer Boehringer-Ingelheim, and Daiichi-Sankyo. He has served on scientific advisory boards for Bayer, Boehringer-Ingelheim, BMS/Pfizer, MindMaze, the editorial board of Stroke. He has received an educational grant from Pfizer and research support from the Science Funds of the University Hospital Basel, the University Basel, the Swiss Heart Foundation and the Swiss National Science Foundation.

KN received speaker's fees from Abbott.

MA received Speaker honoraria from Bayer, Boehringer-Ingelheim, and Covidien; Scientific advisory board honoraria from Amgen, Bayer, Boehringer-Ingelheim, BMS, Pfizer, Covidien, Daichy Sankyo and Nestlé Health Science. Research grants from the Swiss Heart Foundation and the Swiss National Science Foundation.

UF has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation and Medtronic; he is a consultant for Medtronic, Stryker, and CSL-Behring.

PM received speaker honoraria from Medtronic, Stryker. Consultant for Medtronic, Cerenovus, Phenox, Microvention, research grants from the Swiss Heart Foundation, Siemens and iSchemview.

MG reports grants from Bangerter-Rhyner-Foundation.

JK reports grants from the Swiss Stroke Society and the Swiss Academy of Medical Sciences/Bangerter Foundation.

PM has received has received through his institution research grants from the Swiss National Science Foundation, the Swiss Heart Foundation and the ERISTA program (Pfizer/BMS); consulting fees from Medtronic. All this support goes to his institution for stroke education and research.

CWC has received modest honoraria for scientific advisory board from Bayer, Boehringer-Ingelheim and iSchemaview; Research grants from the Swiss Heart Foundation.

MB has received honoraria for travel from Bayer and for participation in advisory board from AstraZeneca.

GK has received modest honoraria for travel and advisory board from Bayer, Medtronic, Alexion, Bial, Boehringer-Ingelheim and Zambon, a research grant from the Swiss Heart Foundation, Swiss Parkinson Foundation, Swiss National Science Foundation.

ARL has received modest honoraria for travel and advisory board from Bayer, Moleac and Amgen and research grants from the P&K Pühringer-Foundation.

SW received research funds by the Swiss National Science Foundation, the UZH Clinical research priority program (CRPP) stroke, the Swiss Heart foundation, Boehringer-Ingelheim, speakers honorarium from Amgen and a consultancy fee from Bayer.

NP has received research funding from the Swiss Heart Foundation and the Swiss National Science Foundation, speaker honoraria from Vifor; served on advisory boards for Bayer, Boehringer-Ingelheim, BMS/Pfizer, Daiichi-Sankyo and AstraZeneca.

FM has received research support from the Swiss Heart Foundation and has not received any honoria from industry 2017.

CBe received modest honoraria for travel and advisory board from Novartis and Bayer.

CBo reports travel and speaker honoraria from Amgen, Bayer, Biogen, Boehringer-Ingelheim, Bristol-Myers-Squibb, Lilly, Merck, Novartis, Pfizer, Roche, Servier, Sanofi, TEVA.

LHB has received grants from the Swiss National Science Foundation, the University of Basel, the Swiss Heart Foundation, and the "Stiftung zur Förderung der gastroenterologischen und allgemeinen klinischen Forschung sowie der medizinischen Bildauswertung". Unrestricted research grant from AstraZeneca, consultancy or advisory board fees or speaker's honoraria from Amgen, Bayer, Bristol-Myers-Squibb, Claret Medical, and InnovHeart, and travel grants from AstraZeneca and Bayer.

Supplemental Materials

Supplemental Table I-II, Supplemental Appendix

References

1. IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. Lancet. 2012;379:2352-2363.
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;72:1019.
3. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med 2018;378:11.
4. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med. 20199;380:1795-1803.
5. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344-e418.
6. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med. 2018;379:611-622.
7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al. Thrombectomy

for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. N Engl J Med. 2018;378:708-718.

8. Ringelstein EB, Chamorro A, Kaste M, Langhorne P, Leys D, Lyrer P, Thijs V, Thomassen L, Toni D; ESO Stroke Unit Certification Committee. European Stroke Organisation recommendations to establish a stroke unit and stroke center. Stroke. 2013;44:828-840.
9. Reuter B, Sauer T, Gumbinger C, Bruder I, Preussler S, Hacke W, Hennerici MG, Ringleb PA, Kern R, Stock C; Stroke Working Group of Baden-Wuerttemberg. Diurnal Variation of Intravenous Thrombolysis Rates for Acute Ischemic Stroke and Associated Quality Performance Parameters. Front Neurol. 2017;8:341.
10. Zonneveld TP, Curtze S, Zinkstok SM, Gensicke H, Moulin S, Scheitz JF, Seiffge DJ, Hametner C, Heldner MR, Traenka C, et al. Non-office-hours admission affects intravenous thrombolysis treatment times and clinical outcome. J Neurol Neurosurg Psychiatry. 2018;89:1005-1007.
11. Helsinki Stroke Thrombolysis Registry Group. Does time of day or physician experience affect outcome of acute ischemic stroke patients treated with thrombolysis? A study from Finland. Int J Stroke. 2012;7:511-6.
12. Darehed D, Blom M, Glader EL, Niklasson J, Norrving B, Bray BD, Eriksson M. Diurnal variations in the quality of stroke care in Sweden. Acta Neurol Scand. 2019;140:123-130.
13. Bray BD, Cloud GC, James MA, Hemingway H, Paley L, Stewart K, Tyrrell PJ, Wolfe CD, Rudd AG; SSNAP collaboration. Weekly variation in health-care quality by day and time of admission: a nationwide, registry-based, prospective cohort study of acute stroke care. Lancet. 2016;388:170-177.
14. Manno C, Disanto G, Bianco G, Nannoni S, Heldner M, Jung S, Arnold M, Kaesmacher J, Müller M, Thilemann S, et al. Outcome of endovascular therapy in

stroke with large vessel occlusion and mild symptoms. Neurology. 2019;93:e1618-e1626.

15. Waje-Andreassen U, Nabavi DG, Engelter ST, Dippel DW, Jenkinson D, Skoda O, Zini A, Orken DN, Staikov I, Lyrer P. European Stroke Organisation certification of stroke units and stroke centres. Eur Stroke J. 2018;3:220-226.
16. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke 1994;25:2220–2226.
17. Fluri F, Hatz F, Voss B, Lyrer PA, Engelter ST. Restenosis after carotid endarterectomy: significance of newly acquired risk factors. Eur J Neurol. 2010;17:493–498.
18. Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. Stroke. 2005;36:777-781.
19. Wright PR, Haynes A, Markovic M. secuTrialR: Seamless interaction with clinical trial databases in R. J Open Source Softw. 2020;5:2816.
20. Kristiansen NS, Mainz J, Nørgård BM, Bartels PD, Andersen G, Johnsen SP. Off-hours Admission and Acute Stroke Care Quality: A Nationwide Study of Performance Measures and Case-Fatality. Stroke. 2014;45:3663-9.
21. Jauss M, Schütz HJ, Tanislav C, Misselwitz B, Rosenow F. Effect of daytime, weekday and year of admission on outcome in acute ischaemic stroke patients treated with thrombolytic therapy. Eur J Neurol. 2010;17:555-561.
22. Campbell JT, Bray BD, Hoffman AM, Kavanagh SJ, Rudd AG, Tyrrell PJ; Intercollegiate Stroke Working Party. The effect of out of hours presentation with acute stroke on processes of care and outcomes: analysis of data from the Stroke Improvement National Audit Programme (SINAP). PLoS One. 2014;9:e87946.

23. Mpotsaris A, Kowoll A, Weber W, Kabbasch C, Weber A, Behme D. Endovascular stroke therapy at nighttime and on weekends-as fast and effective as during normal business hours?. J Vasc Interv Neurol. 2015;8:39-45.
24. Wilson TA, Leslie-Mazwi T, Hirsch JA, Frey C, Kim TE, Spiotta AM, Leacy R, Mocco J, Albuquerque FC, Ducruet AF, et al. A multicenter study evaluating the frequency and time requirement of mechanical thrombectomy. J Neurointerv Surg. 2018;10:235-239.
25. Hajdu SD, Kaesmacher J, Michel PP, Sirimarco G, Knebel JF, Bartolini B, Kurmann CC, Puccinelli F, Mosimann PJ, Bonvin C, et al. Association of Time of Day When Endovascular Therapy for Stroke Starts and Functional Outcome. Neurology. 2021;96:e1124–36.
26. Regenhardt RW, Mecca AP, Flavin SA, Boulouis G, Lauer A, Zachrison KS, Boomhower J, Patel AB, Hirsch JA, Schwamm LH, et al. Delays in the Air or Ground Transfer of Patients for Endovascular Thrombectomy. Stroke. 2018;49:1419-1425.
27. Williams MM, Wilson TA, Leslie-Mazwi T, Hirsch JA, Kellogg RT, Spiotta AM, De Leacy R, Mocco J, Albuquerque FC, Ducruet AF. The burden of neurothrombectomy call: a multicenter prospective study. J Neurointerv Surg. 2018;10:1143-1148.
28. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, Arnold M, Heldner MR, Jung S, Carrera E, et al. Prior Anticoagulation in Patients with Ischemic Stroke and Atrial Fibrillation. Ann Neurol. 2021;89:42-53.
29. Zhou Y, Li W, Herath C, Xia J, Hu B, Song F, Cao S, Lu Z. Off-Hour Admission and Mortality Risk for 28 Specific Diseases: A Systematic Review and Meta-Analysis of 251 Cohorts. J Am Heart Assoc. 2016;5:e003102.
30. Sartini C, Whincup PH, Wannamethee SG, Jefferis BJ, Lennon L, Lowe GD, Welsh P, Sattar N, Morris RW. Associations of time of day with cardiovascular disease risk

factors measured in older men: results from the British Regional Heart Study. BMJ Open. 2017;7:e018264.

Figure Legends

Figure 1: Modified Rankin Scale (mRS) at 3 months. **A** mRS at 3 months in all ischemic stroke patients. **B** mRS at 3 months in ischemic stroke patients treated with acute reperfusion therapy.

Figure 2: Performance measures over time (years).

Figure 3: Rate of wake-up strokes with acute reperfusion treatment.

Table 1. Baseline characteristics of all ischemic stroke patients.

	Stroke Center		Stroke Unit	
	Office hours	**Non-office hours**	**Office hours**	**Non-office hours**
Patients, n(%)	11‘844 (48.7)	12’471 (51.3)	3‘919 (52.4)	3‘554 (47.6)
Demographics				
Age, years, median[IQR]	75 [65-83]	75 [63-83]	76 [66-84]	75 [63-83]
Male sex, n(%)	6739 (57.0)	7145 (57.4)	2170 (55.5)	2036 (57.3)
Independent prior to stroke (pre-mRS 0-2), median[IQR]	9091 (88.1)	9745 (88.9)	2909 (89.3)	2657 (90.0)
Stroke characteristics				
NIHSS, median[IQR]	4 [1-9]	4 [2-11]	3 [1-6]	3 [1-7]
NIHSS, patients with acute reperfusion therapy, median[IQR]	9 [4-16]	9 [5-16]	6 [3-11]	6 [4-12]
Onset-to-admission time, min, median[IQR]	276 [86-982]	208 [81-645]	510 [108-1330]	238 [85-766]
Medical history				
Hypertension, n(%)	8676 (74.7)	8996 (73.5)	2863 (76.9)	2560 (75.9)
Diabetes mellitus, n(%)	2347 (20.2)	2495 (20.4)	802 (21.5)	752 (22.3)
Coronary artery disease, n(%)	2040 (17.7)	2217 (18.2)	598 (16.8)	610 (18.8)
Atrial fibrillation, n(%)	3031 (24.8)	2791 (24.0)	816 (22.0)	779 (23.2)
Prior stroke, n(%)	2168 (18.7)	2274 (18.6)	657 (17.7)	617 (18.3)
Systolic blood pressure, mmHg, median[IQR]	153 [137-172]	155 [138-175]	160 [140-180]	160 [141-180]
Glucose, mmol/l, median[IQR]	6.3 [5.5-7.6]	6.5 [5.7-7.9]	6.3 [5.5-7.6]	6.5 [5.7-8.0]
Medication				
Prior anticoagulation, n(%)	1755 (21.7)	1872 (22.0)	486 (17.8)	477 (19.5)

Table 2. Thrombolysis rate and performance measures.

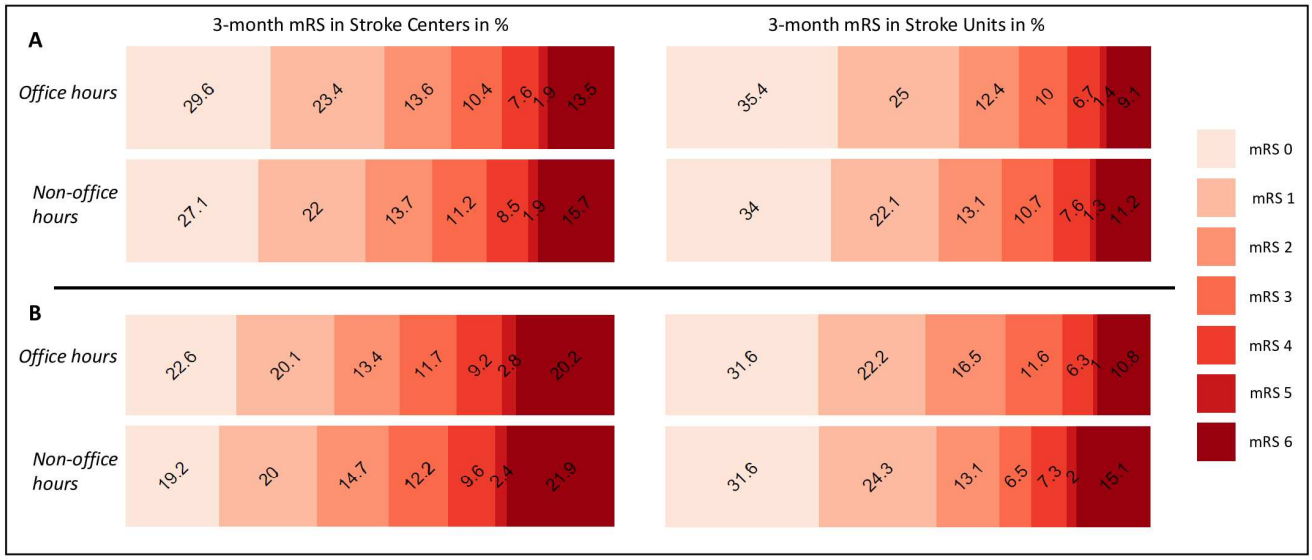
		Office hours	Non-office hours	Office vs non-office hours, p-value
Acute reperfusion therapy, n(%)[a]	Stroke Center	4‘322 (36.5)	5’090 (40.8)	<0.001
	Stroke Unit	724 (18.5)	773 (21.8)	<0.001
Door-to-image time, min, median(IQR)[b]	Stroke Center	22 (16-30)	23 (17-31)	<0.001
	Stroke Unit	17 (11-25)	19 (13-27)	<0.01
Door-to-IVT time, min, median(IQR)	Stroke Center	37 (27-54)	43 (30-61)	<0.001
	Stroke Unit	39 (29-53)	45 (32-65)	<0.001
Door-to-EVT time, min, median(IQR)	Stroke Center	84 (59-116)	95 (66-130)	<0.001

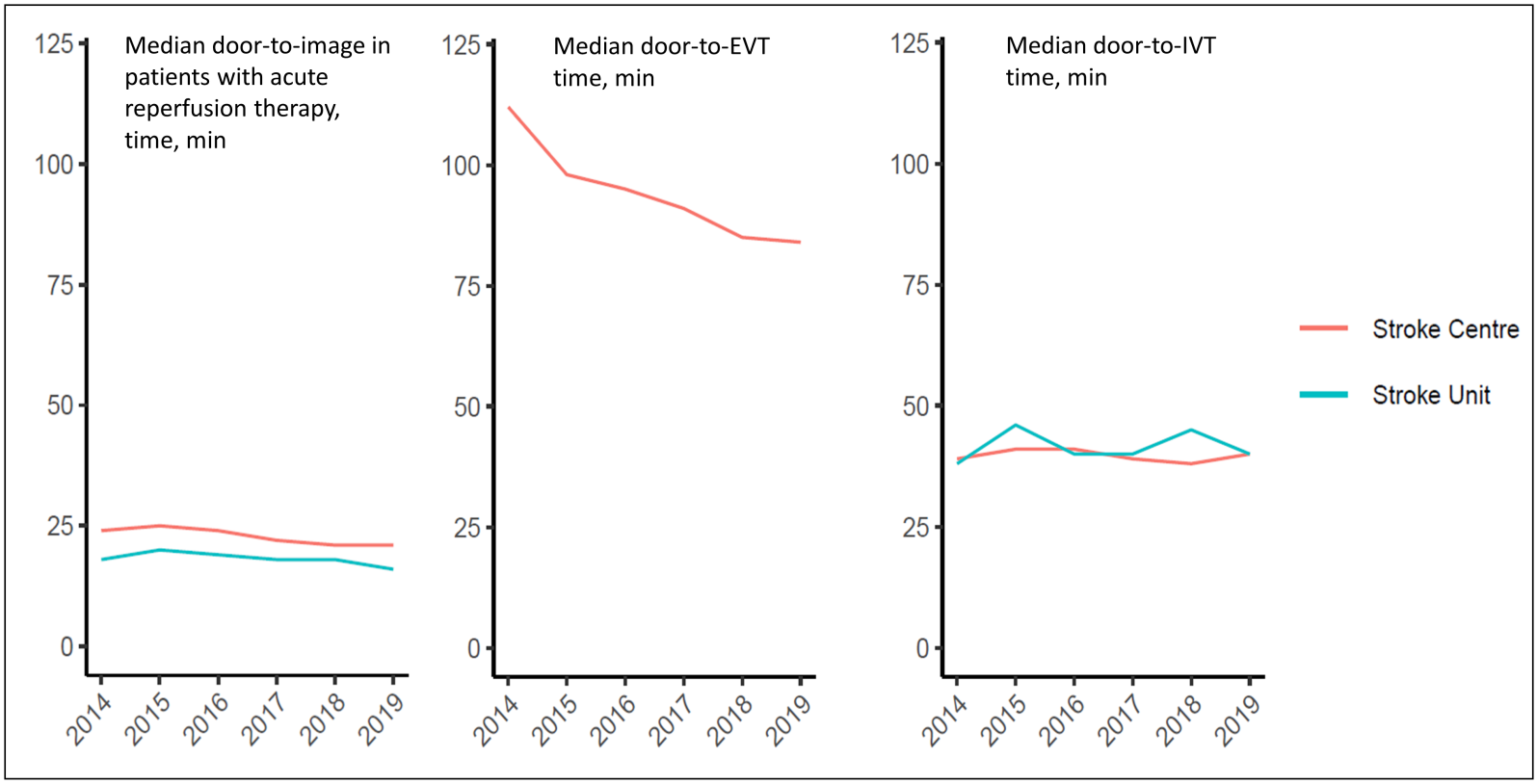
[a] including wake-up strokes [b]in patients treated with acute reperfusion therapy

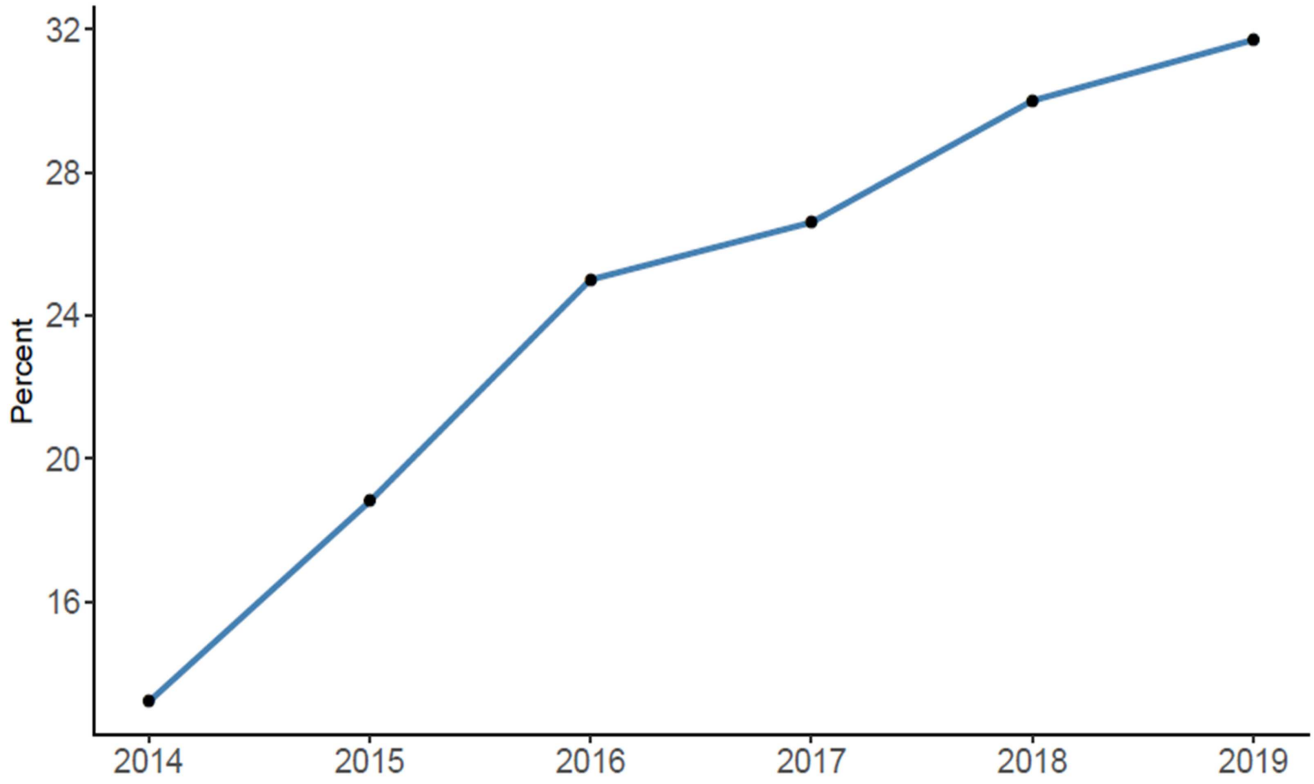
Table 3. Multivariable analysis of outcomes. Odds ratio (95% confidence interval), p-value.

			Worse outcome	Mortality
All ischemic stroke patients[1]	Non-office hours vs office hours	Stroke Center	1.11 (1.04-1.18)[1] p=0.002	1.13 (1.01-1.27)[1] p=0.036
		Stroke Unit	1.12 (0.99-1.26)[1] p=0.078	1.15 (0.89-1.49)[1] p=0.291
Ischemic stroke patients with acute reperfusion therapy[2]	Non-office hours vs office hours	Stroke Center	1.18 (1.07-1.31)[2] p<0.001	1.18 (1.01-1.38)[2] p=0.034
		Stroke Unit	1.12 (0.87-1.46)[2] p=0.374	1.48 (0.89-2.47)[2] p=0.131

Adjusted for: 1 Age, baseline NIHSS, pre-mRS; 2 Age, baseline NIHSS, pre-mRS, onset-to-treatment time


A
3-month mRS in Stroke Centers in %
3-month mRS in Stroke Units in %
Office hours
29.6
23.4
13.6
10.4
7.6
1.9
13.5
35.4
25
12.4
10
6.7
1.4
9.1
Non-office hours
27.1
22
13.7
11.2
8.5
1.9
15.7
34
22.1
13.1
10.7
7.6
1.3
11.2
B
Office hours
22.6
20.1
13.4
11.7
9.2
2.8
20.2
31.6
22.2
16.5
11.6
6.3
1
10.8
Non-office hours
19.2
20
14.7
12.2
9.6
2.4
21.9
31.6
24.3
13.1
6.5
7.3
2
15.1
mRS 0
mRS 1
mRS 2
mRS 3
mRS 4
mRS 5
mRS 6


Median door-to-image in patients with acute reperfusion therapy, time, min
Median door-to-EVT time, min
Median door-to-IVT time, min
125
100
75
50
25
0
2014
2015
2016
2017
2018
2019
Stroke Centre
Stroke Unit


32
28
24
20
16
Percent
2014
2015
2016
2017
2018
2019